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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,722	07/10/2006	Rosanne M Crooke	BIOL0004USA	6604

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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
GIBBS, TERRA C	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,722	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2005 and 16 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *61-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Preliminary Amendments filed October 14, 2005 and February 16, 2006.

Claims 1-60 have been canceled. New claims 61-83 are acknowledged.

Claims 61-83 are pending in the instant application.

Claims 61-83 have been examined on the merits.

Information Disclosure Statement

It is noted that Applicants have not filed an information disclosure statement under § 1.97(c). Applicant is reminded of 37 CFR § 1.56, which details Applicants duty to disclose all information known to be material to patentability.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Applicant's reference to priority in the first sentence of the specification is also acknowledged. It is noted that the instant application is a national stage entry of PCT/US04/10946, filed April 15, 2004, which is a continuation-in-part of USSN 10/418,780, filed April 16, 2003. It is further noted that the reference should be updated to reflect applications for patents that are pending.

The instant application has been afforded priority to July 10, 2006, which is the filing date of the instant application because support for a method of ameliorating

hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III is only found in the instant application, but not in any application that Applicants claim priority to.

In summary, support for a method of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III is only found in the instant application, but not in any other application which Applicants claim priority to. While it is noted that parent applications PCT/US04/10946 and USSN 10/418,780 have support for methods of reducing hyperlipidemia, and lowering serum triglyceride and cholesterol levels in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III, these methods do not support, implicitly or explicitly, ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, or reducing adipose tissue. Therefore, the instant application has been afforded priority to July 10, 2006, which is the filing date of the instant application.

If Applicants believe that they are entitled to an earlier priority date, the Examiner urges Applicant to specifically point where support can be found for the limitations, "hepatic steatosis", "lowering liver tissue triglyceride levels", and "reducing adipose tissue" in any other applications Applicants claim priority to.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 61-83 are provisionally rejected under the judicially created doctrine of double patenting over claims 23, 38, 39, 45-62 and 64 of copending Application No. US Publication No. 20040208856 ('856).

Although the conflicting claims are not identical, they are not patentably distinct from each other because: Claims 61-83 of the instant application are drawn to methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4); wherein the antisense compound comprises chemical modifications thereof. Claims 23, 38, 39, 45-62 and 64 of copending Application No. '856 are drawn to a method of treating an animal having hyperlipidemia; a method of delaying the onset of hyperlipidemia; and methods of lowering cholesterol or triglyceride levels comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4); wherein the antisense

compound comprises chemical modifications thereof. It is noted that the instant application discloses, "For therapeutics, an animal, preferably a human, suspected of having a disease or disorder which can be treated by modulating the expression of apolipoprotein is treated by administering antisense compounds" (see page 28 and 29). The instant specification also discloses that cholesterol levels are plasma or serum levels (see page 4 and Example 21, respectively); triglycerides levels are plasma or serum levels (see pages 3 and 4 and Example 21); the antisense if fully complementary to the target (see page 9); the antisense is 18, 19, 20, 21, or 22 nucleotides in length (see page 13); and the antisense compound demonstrates a reduction in apolipoprotein C-III mRNA levels of at least 45% when applied *in vitro* to cultured HepG2 cells (see Examples 1 and 2 and pages 83 and 85).

Since the method steps recited in the instant application are exactly the same as the method steps recited in copending application '856, claims 23, 38, 39, 45-62 and 64 of co-pending application '856 reads on and fully embraces the methods as instantly claimed and thus fully encompasses the subject matter of the instant application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 61-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising the intraperitoneal injection of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:11), does not reasonably provide enablement for methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising any route of administration of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to methods of ameliorating hepatic steatosis, lowering liver

tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4).

The specification teaches, by way of example, methods of ameliorating hepatic steatosis and lowering liver tissue triglyceride levels in an animal, comprising administering a therapeutically effective amount of antisense compounds that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:11) (see Example 28). Specifically, Example 28 teaches that intraperitoneally injected ISIS 167880 (SEQ ID NO:117), ISIS 167875 (SEQ ID NO:113), ISIS 167878 (SEQ ID NO:115), and ISIS 167879 (SEQ ID NO:116) significantly lowered liver tissue triglyceride levels in animals when compared to saline-treated control animals. It is noted that the term "hepatic steatosis" has been referred to as the accumulation of lipids in the liver (see the instant specification at page 102) and thus the lowering of liver triglyceride levels in liver tissue amounts to ameliorating hepatic steatosis as claimed. The specification also teaches, by way of example, a method of reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of antisense compounds that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:11) (see Example 27). Specifically, Example 27 teaches that intraperitoneally injected, ISIS 167880 (SEQ ID NO:117), ISIS 167875 (SEQ ID NO:113), ISIS 167878 (SEQ ID NO:115), and ISIS 167879 (SEQ ID NO:116) significantly reduced fat pad weight in animals when compared to saline-treated control

animals. It is noted that 167880 (SEQ ID NO:117), ISIS 167875 (SEQ ID NO:113), ISIS 167878 (SEQ ID NO:115), and ISIS 167879 (SEQ ID NO:116) are all targeted to a nucleic acid molecule encoding mouse apolipoprotein C-III (SEQ ID NO:11) (see pages 76-78 and Table 2).

The first issue is that there is no guidance in the specification to suggest that methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising the intraperitoneal injection of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:11) would be effective to result in methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4). As discussed, for example, in Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81) it is unpredictable to determine the antisense ability of an oligonucleotide to inhibit target gene expression based purely on complementarity to a target mRNA. For example, Agrawal et al. teach, "The initial step in selecting an antisense oligonucleotide is to choose an appropriate target sequence on the mRNA molecule. Antisense technology has been hampered to some extent by limited knowledge as to the base-pairing accessibility of mRNA target sites *in vivo*. Although a number of models that predict RNA folding are available, their use-fullness for predicting the most plausible *in vivo* RNA structure is limited" (see page 76, last paragraph). Agrawal et al. go on to teach,

"The affinity of an oligonucleotide for its target RNA varies significantly depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence" (see page 77, second column, first paragraph). Therefore, the feasibility of antisense therapy for one antisense does not demonstrate the feasibility of antisense therapy for a wholly different antisense oligonucleotide, since the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence.

The second issue is that the claims are so broad to include systemic delivery of antisense compounds that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III, where the prior art teaches that systemic delivery of oligonucleotides *in vivo* is highly unpredictable. For example, Nielsen, PE (Gene Therapy, 2005 Vol. 12:956-957) reviews the problems associated with nucleic acid-based therapeutics and systemic delivery. Nielsen, PE teach, "Many 'solutions' to this problem have been published on the subject during the last decade, but we yet have to see an effective delivery technology" (see page 956, second paragraph). Nielsen, PE also discuss that a major unmet challenge for the field is to develop methods that allow effective and simple cellular and especially systemic delivery of antisense agents. Nielsen, PE conclude by discussing the eager anticipation of both academic researchers and the pharmaceutical industry for delivery methods for gene therapy drugs.

In order to practice the invention as claimed, one would first have to establish that the feasibility of antisense therapy for one antisense demonstrates the feasibility of

antisense therapy for a wholly different antisense oligonucleotide. Further, the scope of the claims requires knowledge of how to routinely systemically deliver antisense oligonucleotides *in vivo* to result in a therapeutic effect. Due to the scope of the claims, one of skill in the art would be required to undertake extensive trial and error experimentation, with a large number of patients and patient controls, to devise successful methods of ameliorating hepatic steatosis, lowering liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising any route of administration of a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4).

Thus, given the breadth of the claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the absence of working examples, and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 61-83 are rejected under 35 U.S.C. 102(b) as being anticipated by Crooke, RM (Expert Opinion in Biol. Ther., July, 2005 Vol. 5:907-917.

Claims 61-83 are drawn to methods of ameliorating hepatic steatosis, lowering

liver tissue triglyceride levels, and reducing adipose tissue in an animal, comprising administering a therapeutically effective amount of an antisense compound that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III (SEQ ID NO:4). Applicant is reminded that the instant claims have been afforded the priority date of July 10, 2006, which is the filing date of the instant application. For more information, see the section above entitled "Priority".

Crooke discloses that in a murine model, apolipoprotein C-III antisense oligonucleotides have been shown to safely and significantly reduce apolipoprotein C-III mRNA expression, serum triglyceride levels, liver triglyceride levels, and ameliorate steatosis in C57BL/6 mice fed a high-fat diet. Crooke also disclose that similar results were demonstrated in HTG, fructose fed Sprague-Dawley and Zucker rats (see page 912, second column).

It is noted that Crooke is silent regarding whether their method of administering antisense compounds that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III to an animal resulted in reducing adipose tissue. However, the burden of establishing whether the method disclosed by Crooke would have the additional function of reducing adipose tissue under generally any assay conditions falls to Applicant. See MPEP 2112.01, "Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products

of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433." See also MPEP 2112: "[T]he PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing *In re Fitzgerald* 205 USPQ 594. 596, (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the method of administering antisense compounds that specifically hybridizes with a nucleic acid molecule encoding apolipoprotein C-III to an animal as disclosed by Crooke would or would not reduce adipose tissue as instantly claimed.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg
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